Combinatorial references

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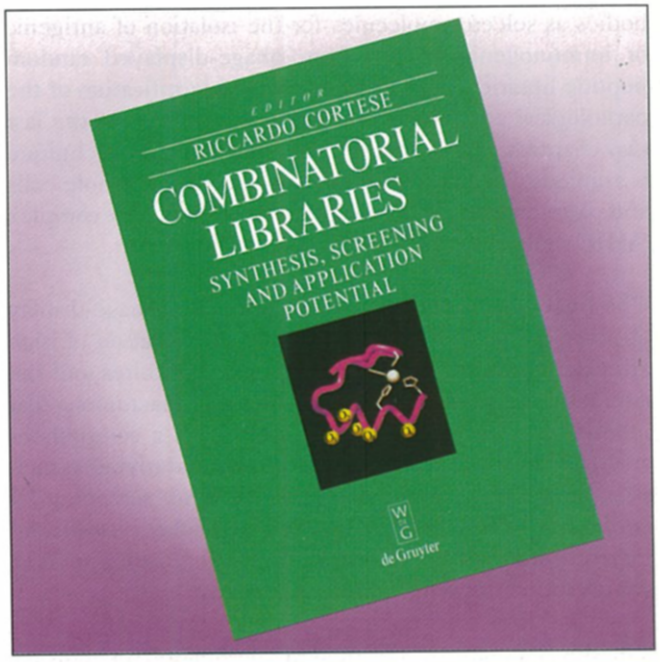
Combinatorial Libraries: Synthesis, Screening and Application Potential edited by Riccardo Cortese, Walter de Gruyter, Berlin and New York, 1996. 232 pp. $102.25 (hardcover) ISBN3-11-014395-X.



Few novel developments in chemistry and molecular biology currently attract as much attention as combinatorial techniques. Combinatorial chemistry emerged first in the late 1980s when a handful of peptide chemists set out to develop methods to generate libraries of thousands of different new compounds in the time it previously took them to synthesize a single molecule. Nowadays, combinatorial techniques are developed and applied in many diverse research fields ranging from organic chemistry to molecular genetics. The enormous interest this subject has for academic and industrial research groups is illustrated by the dozens of scientific meetings, new journals and startup companies in the area, and the exponential increase of publications devoted to it. The development of new concepts based on combinatorial methods is rapid. The application of combinatorial methods to the development of novel drugs and diagnostics, and the use of combinatorial libraries as research tools in life sciences, and even materials sciences, is just starting and forthcoming developments are unpredictable. But there are now a number of well developed concepts that make a book worthwhile. *Combinatorial Libraries: Synthesis, Screening and Application Potential*, edited by Riccardo Cortese, is one of the first monographs intended to cover a broad spectrum of ideas and applications.

So what's it all about, then? The book consists of 12 chapters "presented by scientists who are among the leaders in their respective area of research." The topics covered are separated into four sections. Section A, 'Synthetic peptide libraries,' contains three chapters covering soluble synthetic combinatorial peptide libraries, synthesis, screening and structure determination of non-peptide synthetic structures, and peptide libraries bound to cellulose membranes. This section provides a stimulating introduction to the general concept of combinatorial peptide library constructions and screening techniques and might be particularly useful for newcomers to the field. Chapter 2 is the only chapter dealing with small-molecule libraries and coding techniques. It focuses, however, exclusively on the 'one-bead one-structure' technique performed in the authors' laboratory and only briefly mentions other interesting concepts of small-molecule encoded combinatorial chemistry developed by other research groups. Nevertheless it conveys a good idea of this topic. Section B, 'Nucleic acid libraries," contains two chapters that provide excellent reviews on *in vitro* selection of aptamers and the characterization of an aptamer which bind to and inhibits human thrombin. Chapter 4 in particular is intriguing; as well as reviewing the state of the art in aptamer technology, it discusses very interesting questions such as the abundance of functional sequences in sequence space ("the complexity of complexity") and suggestions on how to improve current technology to select extremely tight binding sequences. When reading Chapter 5, fasten your seat belt! It is a most impressive and comprehensive ride through the characterization and application of a protein inhibitor isolated by combinatorial techniques — a masterly achievement. For those who still need to be convinced, this chapter shows that these techniques can indeed lead to products.

The remaining seven chapters of the book are dedicated to phage-display techniques and are sub-divided into two sections, C and D. Section C, 'Phage display of peptide libraries,' consists of four chapters (6–10) dealing with different variations of peptide libraries displayed on phage. Chapter 6 is an excellent introduction to the concepts of phage-display technology. It contains useful discussions of structural and functional constraints in peptide display on

phage capsids. Chapter 7 deals with conformationally defined phage-displayed peptide libraries, such as antibody fragments or zinc-finger motifs for the display of α-helices. The next chapter describes the use and potential application of human sera instead of monoclonal antibodies as selector molecules for the isolation of antigenic or immunogenic mimics from phage-displayed random peptide libraries. The goal here is the identification of the pathological antigens of autoimmune diseases. In the last two chapters of this section, the phage-display technique is applied to select peptide motifs specific for whole cells and platelets and for the major histocompatibility complex (MHC), respectively.

The final two chapters make up section D, 'Phage display of protein domains.' These describe the isolation of high affinity human antibodies from phage repertoires and the alteration of the function of enzymes and macromolecular inhibitors by phage display. Chapter 11 is a comprehensive and nicely readable survey of the underlying principles of cloning, expression, display, and screening of antibody Fab fragments by the phage display system, and reviews different techniques for randomization of the complementarity-determining regions.

The developments in the field of combinatorial chemistry are occurring much too rapidly to expect that a small monograph like this one would include a complete collection of the various methodologies and concepts of combinatorial techniques. As described above, the book devotes more attention to molecular biological applications than to chemical ones. The editor and authors have done a good job of providing well-written chapters with up-to-date references, covered until 1995. Experts in the field as well as neophytes should learn a lot from this book. Unfortunately, however, it contains a large number of misprints, and there are a number of annoying problems with the references. Many references cited in the main text seem to be missing in the reference list of the related chapters or have been misnumbered. In Chapter 4, for example, some sort of 'frameshift mutation' in the references has crawled in: the text simply does not fit the references provided. These drawbacks will be a major source of confusion to readers who wish to examine the primary literature. They provide reason enough for me to recommend the book only half-heartedly.